Title: Healthy lifestyle index and risk of gastric adenocarcinoma in the EPIC cohort study

Short title: Healthy lifestyle index and gastric cancer risk in EPIC

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Abbreviations:
BMI: Body Mass Index
CI: Confidence Interval
EPIC: European Prospective Investigation into Cancer and Nutrition cohort study
GC: Gastric adenocarcinoma cancer
HR: Hazards Ratio
ICD: International Statistical Classification of Diseases, Injuries and Causes of Death
PAR: Population Attributable Risk
rMED: relative Mediterranean Diet Score
WCRF/AICR: World Cancer Research Fund/American Institute of Cancer Research

Novelty and Impact Statement:

Several modifiable lifestyle factors including smoking, alcohol, certain dietary factors and weight have been independently associated with gastric cancer. However, no study to date has investigated the combined impact of these behaviours, using a healthy lifestyle index, on gastric cancer risk. Our study indicates that adopting a combination of lifestyle behaviours, including not smoking, drinking within alcohol guidelines, following a healthy dietary pattern and having a normal weight dramatically decreases the burden of gastric cancer.

Abstract

Several modifiable lifestyle factors, including smoking, alcohol, certain dietary factors and weight are independently associated with gastric cancer (GC); however, their combined impact on GC risk is unknown. We constructed a healthy lifestyle index to investigate the joint influence of these behaviours on GC risk within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. The analysis included 461,550 participants (662 first incident gastric adenocarcinoma (GC) cases) with a mean follow-up of 11.4 years. A healthy lifestyle index was constructed, assigning 1 point for each healthy behaviour related to smoking status, alcohol consumption and diet quality (represented by the Mediterranean diet) for assessing overall GC and also body mass index for cardia GC, and 0 points otherwise. Risk of GC was calculated using Cox proportional hazards regression models while adjusting for relevant confounders.

The highest versus lowest score in the healthy lifestyle index was associated with a significant lower risk of GC, by 51% overall (HR 0.49 95% CI 0.35, 0.70), by 77% for cardia GC (HR 0.23 95% CI 0.08, 0.68) and by 47% for non-cardia GC (HR 0.53 (95% CI 0.32, 0.87), p-trends<0.001. Population attributable risk calculations showed that 18.8% of all GC and 62.4% of cardia GC cases could have been prevented if participants in this population had followed the healthy lifestyle behaviours of this index.

Adopting several healthy lifestyle behaviours including not smoking, limiting alcohol consumption, eating a healthy diet and maintaining a normal weight is associated with a large decreased risk of GC.

Introduction

Although incidence of gastric cancer (GC) is declining in many countries, it is still the fourth most common malignancy and the second leading cause of death due to cancer worldwide(1). In 2008, more than 990,000 incident cases were recorded (7.8% of new cancers) with 738,000 deaths. In addition, both early diagnosis and effective treatment still remain a challenge. There are a number of modifiable risk factors that are individually related to risk of developing GC, including smoking(2), alcohol drinking(3), dietary factors(4) and weight(5). As behavioural patterns often cluster together in everyday life, it is informative from a public health point of view to examine the combined impact of several lifestyle factors on health outcomes(6-15), especially when considering multi-factorial diseases such as cancer, including GC(4;16).

Smoking is an established risk factor of GC(2) and in previous analyses in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST) there was a 45% higher risk of GC associated with ever compared to never smoking(17). With regards to alcohol, a recent meta-analysis found that heavy consumption was associated with an increased risk but moderate consumption was not(3). This was reflected in subsequent results from EPIC-EURGAST where ≥60g/day of alcohol was associated with a 65% increased risk of GC(18). In addition there is mounting evidence that being overweight or obese is a risk factor for cardia GC, but it has not been associated with total GC, according to a recent meta-analysis including over 10 million people(5).

With regards to diet, although the World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) report concluded that there is as yet no convincing evidence about the relationship between dietary factors and GC, the Panel concluded that food and nutrition may play an important role in the prevention and causation of GC(4). Several foods characteristic of the Mediterranean dietary pattern have been related to a lower risk of GC in EPIC-EURGAST, including a high intake of fruit and vegetables(19) and cereal fibre(20) and low intake of red and processed

meat(21). In addition, we have observed that high adherence to a Mediterranean diet was associated with a 33% reduction in GC in the same population(22).

In summary, there is considerable evidence that several modifiable lifestyle factors are individually associated with risk of GC; however to our knowledge no study has evaluated their combined impact specifically on GC, which is relevant since people's behavioural patterns often cluster. We therefore evaluated the effects of a healthy lifestyle index, combining smoking status, alcohol consumption, diet quality evaluated on the basis of adherence to the Mediterranean dietary pattern and body mass index (BMI) (only in cardia GC analyses), on the risk of developing GC according to tumour site and histological type.

MATERIAL AND METHODS

Study subjects and data collection

EPIC is a prospective cohort study designed to investigate the relationship between nutrition, dietary habits, lifestyle, genetic and environmental factors and cancer and other chronic diseases. It is an on-going cohort study across 23 centres in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom) whose study design has been reported previously(23;24). In brief, 521,454 participants aged mostly 25-70 years old were recruited between 1992 and 2000 mainly from the general population within defined geographical or administrative areas, but with some exceptions(24). All study participants gave written informed consent and ethical approval was obtained from all participating centres and the International Agency for Research on Cancer (IARC).

The habitual diet over the previous year was measured at recruitment through various methods, including validated country-specific questionnaires (semi-quantitative food frequency or diet history questionnaires) or 7-day food records(24;25). Participants also filled in lifestyle questionnaires including information on education, occupation, physical activity, lifetime history of alcohol and tobacco consumption and reproductive and medical history. Anthropometric measures were taken by trained personal, apart from in France, Norway and Oxford where they were self-reported.

Definition of GC cases, study population and follow-up

Vital status was obtained through periodic linkage to regional or national mortality registries. Incident GC cases were identified through population cancer registries, except for France, Germany and Greece where a combination of methods were used, as detailed previously(24). A total of 892 incident GC cases were reported to the central database at IARC up to September 2010. These stomach cancers include cancers coded as C16 (C16.0 for cardia and C16.1-16.6 for non-cardia), according to the 10th Revision of International Statistical Classification of Diseases, Injuries and Causes of Death (ICD). A panel of pathologists confirmed the diagnosis, classification of tumour site and morphology of the tumours for 81% of the cases (according to ICD02 Classification and to Lauren classification for histology)(26). Among the incident cases, 41 gastric lymphomas and 91 other non-adenocarcinoma GC were excluded, leaving 760 gastric adenocarcinomas.

Of the initial 521,454 participants in the EPIC cohort, participants with prevalent cancer at recruitment and with incomplete follow-up (n=28,289) were excluded. Participants with missing dietary and lifestyle data (n=6,253) or with a ratio for energy intake versus energy expenditure in the top and bottom 1% (n=9,600) or missing information for the components used to construct the healthy lifestyle index were also excluded (n=15,762). Therefore, this current analysis is based on data from 461,550 participants, including 662 incident GC.

Healthy lifestyle index construction

An a priori healthy lifestyle index was created based on current scientific knowledge(27) and public health recommendations of dietary/ lifestyle factors that are specifically related to GC(4). The lifestyle factors included i) smoking status, ii) alcohol consumption, and iii) diet quality evaluated with a modified version of the relative Mediterranean diet (rMED) score, which incorporates intakes of fruit, vegetables and meat products (dietary components especially relevant for GC(19;21)), as well as olive oil, legumes, dairy products, fish, seafood and cereals. The rMED score, whose construction has been described previously(22), was modified in this analysis to exclude alcohol since it is evaluated as a separate factor within the index. A fourth factor, BMI (largely reflecting lifestyle choices such as diet

and physical activity) was added to the index for the analyses of cardia GC, since there is strong evidence that being overweight or obese is a risk factor for cardia GC, but it has not been associated with non-cardia GC(5). Each lifestyle factor was scored dichotomously by assigning 1 or 0 points, depending on whether a healthy behaviour was followed or not. The healthy lifestyle behaviours were defined as i) never smoking or quitting >10 years before recruitment, ii) no or low consumption of alcohol (defined as ≤12.5g/d for women and ≤25.0g/d for men) in accordance with the WCRF/AICR guidelines(4), iii) >8 points on the rMED score (ranging from 0-16) and iv) being within a normal weight range (18.5 to <25.0kg/m^2). The overall index was determined by summing all the points obtained from each lifestyle factor, to give an overall score from 0-3 for the overall GC index and 0-4 for cardia GC, with higher points indicating adherence to a greater number of healthy lifestyle behaviours.

Statistical Analyses

Analyses were performed using Stata version 10 (Statacorp, College Station, TX). The cohort's baseline characteristics were assessed in relation to the healthy lifestyle index. The association between the healthy lifestyle index and GC was assessed using Cox proportional hazards regression models, and hazard ratios (HR) and 95% confidence intervals (CI) were calculated. The healthy lifestyle index was modelled as a categorical variable (each point representing a separate category, with 0 points as the reference), and as a continuous variable (for each 1-point increment in score). Age was used as the primary time variable, with entry time defined as age at recruitment and exit time defined as age at diagnosis of first GC for cases and for non-cases age at death, age at diagnosis of cancer other than GC or age at last complete follow-up, depending on which occurred first. All models were stratified by sex and age at EPIC study entry, and by centre to control for country effects. The Cox models were adjusted for total energy intake (Kcal/day, continuous), education level (none, primary, secondary, technical, university, unknown), BMI (<25kg/m^2, ≥25 to <30kg/m^2, ≥30kg/m^2) (except for analyses of cardia GC since BMI is within the index and for non-cardia GC since BMI is not a risk factor) and physical activity level(28) (inactive, moderately inactive, moderately active, active, unknown). Cox models were run to assess the association between the entire healthy lifestyle index and overall GC, and GC by anatomical site (cardia/non-cardia) and histological type

of the tumours (intestinal/diffuse). The Wald statistic(29) was carried out to assess the homogeneity of risk by location and histologic type for each 1-point increment in score. Sex-specific models were fitted and effect modification by sex was tested using the log likelihood ratio test. Separate models were also fitted for each of the healthy lifestyle factors within the index (modelled as a binary variable with the unhealthy behaviour (0 points) as the reference), while mutually adjusting for the remaining lifestyle factors and also the potential confounding variables mentioned above. All models were tested for and satisfied the proportional hazards assumption.

Population attributable risk (PAR) fractions(30) were estimated to quantify the proportion of GC cases that could have been avoided, assuming a causal relationship, if all the studied population had been in the healthiest category for all the healthy lifestyle behaviours within the index. The formula used(31) takes into account the observed multivariate adjusted hazard ratios of GC for category within healthy lifestyle index, and the prevalence of the exposure within the cases. Point estimates were calculated using the formula described by Rockhill et al(31) and bootstrap sampling (repeated 1000 times) was used to calculate the 95% CIs.

Sensitivity analyses

In sensitivity analyses physical activity was also incorporated into the healthy lifestyle index, since there is some evidence, albeit not conclusive(4), that physical activity might be associated with GC(32). A score of 0 was given to participants who were inactive or moderately inactive and 1 point to those who were moderately active or active (37,469 participants had unknown physical activity level and were excluded from this sensitivity analysis). In addition, the main models were repeated excluding the adjustment for physical activity, which may in part be an intermediate factor between established risk factors included in the index. Separate models were also created stratifying by level of educational attainment (none and primary school versus secondary school and above), to explore any potential differences in risk by education and its related factors. A further sensitivity analysis included waist circumference in the index instead of BMI, defined according to ATPIII criteria(33); 0 points for a waist circumference >102cm for men and >88cm for women, and 1 point for a waist circumference below these sex specific cut-offs. The analyses were also repeated excluding i) the first two years of follow-up, in order to exclude GC cases

identified during this period, as they could have had pre-diagnostic symptoms which might have changed their dietary or lifestyle habits ,and ii) probable dietary miss-reporters (157,232 participants including 214 GC cases excluded), defined using Goldberg criteria(34), to reduce BMI-related under-reporting.

RESULTS

During a mean follow-up of 11.4 (standard deviation 2.5) years, corresponding to 5,097,499 accumulated person-years, a total of 662 GC (60% men) were identified among the 461,550 (30% male) participants. The distribution of cases across EPIC countries is shown in Table 1. The GC cases were classified according to their anatomical site, with 192 (29%) cases in the cardia, 315 (48%) cases in the distal stomach region (non-cardia) and 155 (23%) cases with an unknown location. According to the Lauren classification there were 213 (32%) diffuse GC, 197 (30%) intestinal GC and 252 (38%) cases with unknown histological type. Participants with a higher healthy lifestyle score were more likely to be female, and to have a lower total energy intake and lower physical activity level but a higher BMI (Table 2).

The association between each individual lifestyle factor and risk of overall GC by anatomical location is shown in Table 3. Never smoking or quitting more than 10 years previously compared to smokers was associated with a decreased risk of overall GC (HR 0.64, 95% CI 0.54, 0.75), non-cardia GC (HR 0.67,95% CI 0.53, 0.86) and cardia GC (HR 0.56, 95% CI 0.41, 0.75). There was also a strong inverse association between alcohol intake (within compared to outside the recommended range) and overall GC, especially non-cardia GC (HR 0.74, 95% CI 0.56, 0.97), but no association was observed for cardia GC. In contrast, a high compared to low rMED score was only significantly related to cardia GC (HR 0.61, 95% CI 0.38, 0.97). Finally, for BMI (only included in the index for cardia GC analyses) a normal compared to non-normal weight was not associated with overall or non-cardia GC, but there was a lower, albeit non-significant, risk of cardia GC.

The overall healthy lifestyle index was related to a large significant reduction in GC risk, reaching a 51% (95% CI 30% to 65%) lower risk associated with participants scoring 3 points (following all three healthy behaviours) compared to none (Table 4). Although this inverse association was stronger and only significant in men compared

to women, there was no evidence of effect modification by sex (p=0.767). The results by anatomical site showed the strongest association for cardia GC, with a 77% (95% CI 32, 92%) reduction associated with following all four healthy lifestyle behaviours(including a normal BMI) compared to none. There was no evidence of heterogeneity between cardia and non-cardia though (P=0.468). The results by histological type showed around a 50% significant lower risk of both diffuse and intestinal GC for participants with the highest score (P for heterogeneity = 0.877). The associations between each 1 point increment in the healthy lifestyle index and GC risk (overall and by location and type) were all significant (Table 4),with a 25% (p-trend <0.001) lower risk for overall GC.

The PAR, proportion of GCs that could have been avoided if the entire cohort followed the healthiest behaviours in the index, was 18.8% (95% CI 0.2, 35.0) for all GC cases, 62.4% (95% CI 15.4, 90.2) for cardia GC and 10.2% (95% CI 16.4 , 33.0) for non-cardia GC. In sensitivity an analysis excluding the first two years of follow up there was a similar reduction in risk of GC associated with following all three healthy lifestyle behaviours compared to none (HR 0.53, 95% CI 0.32, 0.87). The risk estimates were slightly de-attenuated after excluding dietary miss-reporters from the analyses (for overall GC HR 0.40, 95% CI 0.27, 0.61 for 3 versus 0 points) and after adding physical activity to the index, particularly for non-cardia GC (HR 0.38, 95% CI 0.20, 0.75). Only marginal changes in risk estimates were observed when waist circumference was substituted for BMI within the index and when physical activity was excluded from the covariates in the main Cox models (data not shown). The risk estimates for GC for each 1-unit increase in the index were similar for participants with a lower (HR 0.77 95% CI 0.66, 0.90) compared to higher (HR 0.72 95% CI 0.63, 0.88) educational attainment.

DISCUSSION

This large European prospective cohort study found that a high score on a healthy lifestyle index, based on key modifiable lifestyle behaviours related to GC aetiology, was associated with an approximately 50% lower risk of GC. The magnitude of the association was more pronounced for cardia GC when BMI was included in the index, with up to a 77% lower risk related to following four healthy lifestyle

behaviours. Assuming a causal relationship, then 19% of all GC cases and 62% of cardia GC could have been prevented in this population if all the participants had followed the healthiest lifestyle behaviours.

These results are particularly relevant for clinical guidelines, taking into account the current limitations of other strategies to prevent GC, such as the treatment or eradication of Helicobacter pylori (Hp) infection; Hp vaccines are a future promise but still not available and massive Hp infection eradication therapy through antibiotics is not feasible or advisable for the general population(27). Consequently, one of the most effective ways to decrease the burden of GC at present appears to be through avoiding exposure to factors that increase risk and promoting factors related to reducing risk, as represented in the modifiable behaviours of the healthy lifestyle index.

As this is the first study to assess the combined impact of associated healthy lifestyle behaviours on GC risk, we cannot directly compare our results with others. However, recent cohort studies have also found that adopting a combination of healthy lifestyle behaviours substantially reduces the risk of overall cancer or other cancers sites (12;13;15;35). For instance, a high healthy lifestyle score was related to a significant 58% decreased risk of pancreatic cancer in the NIH-AARP study(12), a 30% reduction in colorectal cancer in the Danish Diet and Health Cohort Study(13) and a 51% decreased risk of digestive cancers (including stomach) in the French E3N cohort (sub-cohort of EPIC)(35). The Women's Health Initiative Observational Study also found large reductions in cancer risk from adhering to the American Cancer Society healthy lifestyle guidelines, with a significant 17% lower risk of any cancer, 22% lower risk of breast cancer and 52% lower risk of colorectal cancer for a high versus low ACS score(15).

The relationship between GC and the individual lifestyle factors within the index were consistent with previous findings in EPIC(17;18;22) and other studies(2-5). Current smoking appeared to have the greatest individual impact on risk of GC in this present study, in line with high risk attributed to smoking(2;17). Adhering to the Mediterranean diet was related to a lower risk of GC, restricted to cardia GC, while no or low consumption of alcohol was related to a lower risk of GC, particularly non-

cardia GC. However, the impact of following the combined healthy behaviours within the index was stronger than any single behaviour of the index.

We only included modifiable lifestyle behaviours in the index if there was sufficient evidence that they were specifically associated with GC(16;19;21), since the aim of our study was not to explore the effect of following general cancer prevention recommendations of GC risk.(4) This has already been explored within EPIC data[34], where comparing the 5th to the 1st category of the WCRF/AICR based cancer prevention score resulted in a significant 38% decreased risk of GC and 18% decreased risk of developing any cancer(36). Therefore, BMI and physical activity, two important factors related to many other cancer sites(4) and chronic diseases, were not included in the main index due to their non-conclusive associations with overall GC. However, BMI was included in the index for analyses of cardia GC, due to mounting evidence that overweight and obesity are only related to cardia GC but not overall GC(5), as reflected in our results where a normal weight compared to overweight/obesity reduced risk of only cardia GC. In addition, physical activity was included in the index in sensitivity analyses, but this only resulted in a slightly greater reduction in risk of non-cardia GC, in accordance with previous EPIC results(32).

The strengths of this study are its large size, prospective cohort design, long follow-up and detailed dietary and lifestyle exposure data. In addition, we had histologically validated information on different GC anatomic locations and histologic types, which is relevant since they may be etiologically heterogeneous(37). Finally, the robustness of the results was confirmed by the negligible changes in the results in the sensitivity analyses. A study limitation is that the EPIC cohort may be healthier than the general population, since the participants were volunteers. In addition, PARs depend on the relative risk and prevalence of risk factors in the studied population, so caution should be taken when generalising these results to other populations. Another limitation is the construction of the score, which uses dichotomous a priori cut-offs to define ‘healthier’ and ‘less healthy’ behaviours for each lifestyle factor. However, the definition of the healthy behaviours was predominantly based on public health recommendations(2;4) and the advantage of dichotomous compared to continuous scoring is that relevant findings can be more easily translated into clearer public

health recommendations. The index also gives equal weight to each of the lifestyle factors included, although certain factors might be more or less related to GC.

We used an rMED score to represent an overall healthy diet; however processed and red meat, fruit and vegetables are the predominantly relevant dietary components for GC aetiology(19;21), so it could be argued that these should have been included into the lifestyle score directly. However, the advantage of using a dietary score is that it takes into account the complexity of the diet, including dietary interactions and other possibly relevant dietary components. Although we adjusted for potential confounders in the multivariate models, we cannot rule out some residual confounding as the lifestyle variables were mostly self-reported. Finally, Hp infection, an established causal risk factor for GC(4), was not controlled for in the analyses because principal evidence from prospective studies indicate that Hp infection is a necessary condition only in the development of non-cardia GC(38) and is not a risk factor for cardia GC. Therefore, Hp infection should not confound the results stratified by anatomical site, which show a clear negative association between the healthy lifestyle index and risk of cardia GC, (where Hp infection is not a risk factor) and also between the index and non-cardia GC (where Hp infection is a necessary condition in all cases).

Our results indicate that following a combination of modifiable healthy lifestyle behaviours could dramatically decrease the burden of GC. These findings are particularly relevant considering the very poor relative survival rate for GC (25% at 5-years)(39), which is reported to be worse for cardia GC (20% at 5-years) compared to non-cardia GC (31% at 5-years)(40). Understanding the impact of combined lifestyle habits on GC risk further underscores the importance of health promotion strategies to eradicate cigarette smoking, reduce overweight/obesity, limit alcohol consumption if consumed and improve diet quality.

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Table 1. The distribution of participants and gastric cancer cases according to anatomical location and histological type in 10 countries participating in the European Prospective Investigation Into Cancer and Nutrition (EPIC) study cohort[1]

Country	Cohort Sample (% male)	Person-years	Gastric Cancer				
			Total[2] (% male)	Cardia[2]	Noncardia[2]	Intestinal[2]	Diffuse[2]
France	64,078 (0)	667,266	19 (0)	6	10	7	5
Italy	44,271 (31)	497,159	86 (43)	15	54	36	40
Spain	39,868 (38)	480,937	77 (56)	7	51	32	26
United Kingdom	71,844 (40)	800,521	86 (74)	42	25	22	12
The Netherlands	35,142 (36)	415,192	41 (27)	14	18	8	12
Greece	24,671 (41)	234,846	33 (57)	4	18	12	14
Germany	48,027 (44)	474,871	91 (73)	19	51	30	43
Sweden	47,637 (46)	625,067	106 (57)	33	51	26	28
Denmark	53606 (47)	586,240	102 (56)	48	27	23	19
Norway	32,406 (0)	315,400	21 (0)	4	10	1	14
Total	**461,550 (30)**	**5,097,499**	**662 (60)**	**192**	**315**	**197**	**213**

[1] Study centers per country: France (North-East, North-West, South, South coast); Italy (Florence, Varese, Ragusa, Turin, Naples); Spain (Asturias, Granada, Murcia, Navarra, San Sebastian); United Kingdom(Cambridge, Oxford [general and health conscious population]); The Netherlands (Bilthoven, Utrecht); Germany (Heildelberg, Potsdam); Sweden (Umea, Malmö); Denmark (Aarhus, Copenhagen), Norway (North-West and South-East)

[2]The subtypes of GC do not add up to total GCs because cardia and noncardia classifications do not include tumors of unknown or mixed locations (n=155) and intestinal and diffuse classifications do not include unknown, unclassified or mixed morphologies (n=252)

Table 2. Baseline characteristics of the 461,550 participants in the European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort according to the Healthy Lifestyle Index

Characteristics	Total Cohort	Healthy Lifestyle Index [1]				
		0	1	2	3	p-values
No. Participants	461,550	30,907	130,563	200,501	99,579	
No. Gastric Cancer Cases	662	70	239	245	108	
Index Components						
Alcohol, g/day (SD)	11.6 (16.9)	39.0 (24.4)	17.0 (19.7)	7.7 (10.9)	3.9 (4.9)	<0.001
Smoking, % never	44.5	0	14.7	53.7	78.8	<0.001
MD score, mean (SD)	7.8 (3.1)	5.6 (1.9)	6.4 (2.6)	7.6 (2.9)	10.9 (1.6)	<0.001
BMI, kg/m^2, mean (SD)	25.4 (4.3)	25.0 (3.9)	25.2 (4.1)	25.4 (4.2)	25.8 (4.7)	<0.001
Covariates						
Gender, male (%)	29.8	43.7	35.8	29.6	17.9	<0.001
Age at recruitment, mean years (SD)	51.2 (9.9)	51.8 (8.4)	50.9 (9.3)	51.3 (10.1)	51.3 (10.8)	<0.001
Energy intake, mean kcal/day (SD)	2,075 (619)	2,355 (659)	2,152 (651)	2,055 (599)	1,929 (555)	<0.001
Physical activity, % moderate/high activity level	39.5	48	42.2	39.6	33.1	<0.001
Waist circumference, % below ATPIII cut-offs	60.1	68.3	58.1	59.5	61.6	<0.001
Education, % secondary/university education	45.6	49.2	44.1	46.3	45.3	<0.001

Abbreviations; SD: standard deviation. BMI: body mass index. ATPIII: National Cholesterol Education Program's Adult Treatment Panel III

[1] Healthy Lifestyle Index includes three behavioural components; smoking status, Mediterranean diet score and alcohol consumption.

Table 3. Hazard ratios for gastric cancer risk in relation to each single lifestyle factors within the Healthy Lifestyle Index

		All Gastric Cancer			Cardia Gastric Cancer			Non Cardia Gastic Cancer		
Healthy lifestyle index component	**Score**	**No. Cases**	**HR (95% CI)**	**p-value**	**No. Cases**	**HR (95% CI)**	**p-value**	**No. Cases**	**HR (95% CI)**	**p-value**
Smoking										
Current or quit for ≤10y	0	309	1 [Reference]		97	1 [Reference]		141	1 [Reference]	
Never smokers or quit for >10y	1	353	0.64 (0.54, 0.75)	<0.001	95	0.56 (0.41, 0.75)	<0.001	174	0.67 (0.53, 0.86)	0.001
Alcohol consumption[1]										
Moderate/ high intake (women >12.5g/d, men >25g/d)	0	182	1 [Reference]		47	1 [Reference]		90	1 [Reference]	
No/ low intake (women ≤12.5g/d, men ≤25g/d)	1	480	0.83 (0.69, 1.00)	0.058	145	1.08 (0.75, 1.54)	0.682	225	0.74 (0.56, 0.97)	0.027
Mediterranean diet score[2]										
≤ 8 points	0	442	1 [Reference]		155	1 [Reference]		184	1 [Reference]	
> 8 points	1	220	0.87 (0.69, 1.09)	0.220	37	0.61 (0.38, 0.97)	0.035	131	1.11 (0.80, 1.54)	0.539
Body Mass Index[3]										
Overweight/ obese (≥25kg/m$^{2)}$ and underweight (<18.5kg/m$^{2)}$	0	415	1 [Reference]		126	1 [Reference]		202	1 [Reference]	
Normal (18.5 to <25 kg/m^2)	1	247	1.02 (0.86, 1.20)	0.827	66	0.80 (0.59, 1.09)	0.166	113	0.99 (0.77,1.27)	0.928

Cox proportional hazards models mututally adjusted for all components of the healthy lifestyle index and additionally adjusted for physical activity, educational attainment, total energy intake, and stratified by sex, country and age at recruitment.

[1]Acohol intake cutoffs are calculated in accordance with WCRF/AICR guidelines

[2]Mediterranean diet score (0-16 points): based on methodology used in previous EPIC article on MD and gastric cancer (Buckland et al. AJCN. 2009), but excluding alcohol intake.

[3]Body Mass Index: only included in analyses of cardia gastric cancer.

Table 4. Hazard ratios for gastric cancer risk, according to anatomical site and histological type, in relation to the Healthy Lifestyle Index

Gastric Cancer	N Cases	Healthy Lifestyle Index Score (categorical)[1]					Healthy Lifestyle score (+1-point)	P-value trend
		0	1	2	3	4		
All[2]	662	[Reference]	0.78 (0.59, 1.03)	0.50 (0.38, 0.66)	0.49 (0.35, 0.70)	-	0.75 (0.67, 0.83)	<0.001
Men	381	[Reference]	0.69 (0.50, 0.95)	0.44 (0.31, 0.62)	0.42 (0.27, 0.67)	-	0.71 (0.62, 0.81)	<0.001
Women	281	[Reference]	1.02 (0.60, 1.72)	0.64 (0.38, 1.08)	0.66 (0.37, 1.19)	-	0.80 (0.68, 0.94)	0.007
Anatomical site[3]								
Cardia	192	[Reference]	0.79 (0.44, 1.40)	0.64 (0.36, 1.15)	0.42 (0.22, 0.80)	0.23 (0.08, 0.68)	0.74 (0.62, 0.87)	<0.001
Non Cardia	315	[Reference]	0.72 (0.48, 1.10)	0.48 (0.32, 0.74)	0.53 (0.32, 0.87)	-	0.78 (0.67, 0.90)	0.001
Histological type[4]								
Diffuse	213	[Reference]	0.98 (0.58, 1.66)	0.62 (0.36, 1.06)	0.52 (0.27, 0.99)	-	0.75 (0.63, 0.90)	0.002
Intestinal	197	[Reference]	0.66 (0.40, 1.09)	0.37 (0.22, 0.63)	0.49 (0.27, 0.90)	-	0.74 (0.61, 0.89)	0.002

Cox proportional hazards models adjusted by BMI (except in cardia and non-cardia models), physical activity, educational attainment, total energy intake, and stratified by sex, country and age at recruitment.

[1]In analyses of all gastric cancers and non-cardia, diffuse and intestinal subtypes, the healthy lifestyle index includes 3 behavioural components; smoking status, Mediterranean diet score and alcohol consumption. An additional 4th component, BMI, is included in analyses of only cardia gastric cancer.

[2]Test for interaction by sex not significant (p=0.767)

[3]Test for heterogeneity by anatomical location not significant (p=0.468)

[4]Test for heterogeneity by histological type not significant (p=0.877)